REMARKS

Applicant respectfully requests reconsideration. Claims 121-142 were previously pending in this application. No new matter has been added.

Applicant has amended claims 121 and 139-142 to clarify that the C residues in each of the CG dinucleotides recited in SEQ ID NO:246 are unmethylated.

Claims 121-142 are pending for examination with claims 121 and 139-142 being independent claims.

Rejection under 35 U.S.C. §112

Written Description

The Examiner maintained the rejection of claims 121-142 under 35 U.S.C. §112, first paragraph, for lack of sufficient written description. The Examiner asserts that claims 121-142 introduce new matter not sufficiently disclosed in the specification. Applicant respectfully disagrees.

In determining whether an application provides sufficient written description of the claimed invention, "the Examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the original disclosure a description of the invention defined by the claims". MPEP 2163 II 3(b). Applicant asserts that the Examiner has not demonstrated why one of ordinary skill in the art would not envisage the claimed invention from the disclosure presented in the specification.

The written description requirement is satisfied if the invention is described in "sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations ..." MPEP 2163 citing *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). Possession of the invention may be shown in a number of ways including "describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention." MPEP 2163 citing *Regents of the University of California v. Eli Lilly,*

119 F.3d 1559, 1568 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206 (Fed. Cir. 1991). Whether a specification adequately supports a claimed invention is determined on a case-by-case basis because the analysis is particularly factually based. *Vas-Cath*, 935 F.2d at 1561. The specification need not however recite the claimed invention in haec verba. *Lockwood*, 107 F.3d at 1572.

The rejected claims relate to methods for increasing the responsiveness to a cancer therapy by administering an immunostimulatory oligonucleotide comprising the sequence of SEQ ID NO:246 and particular cancer medicaments. These methods and their various limitations are explicitly described in the specification and based on this disclosure one of ordinary skill in the art would recognize that Applicant had possession of the claimed methods. For example, support for administering an oligonucleotide of the claimed invention to increase responsiveness to a cancer therapy such as a chemotherapy can be found on page 14 lines 28-31 which state

> "Py-rich and TG nucleic acids may also be used for increasing the responsiveness of a cancer cell to a cancer therapy (e.g., an anti-cancer therapy), optionally when the Py-rich or TG immunostimulatory nucleic acid is administered in conjunction with an anti-cancer therapy. The anti-cancer therapy may be a chemotherapy ..."

and page 15 lines 11-16, 17, and 32 and page 16 lines 2 and 5 which state

> "... a subject having cancer or at risk of having cancer is administered an immunostimulatory nucleic acid and an anti-cancer therapy. In some embodiments, the anti-cancer therapy is selected from the group consisting of a chemotherapeutic agent ... The chemotherapeutic agent may be selected from the group consisting of ... cisplatin, ... Taxol/paclitaxel, ... doxorubicin, ... Gemcitabine, ... Carboplatin ... "

Support for administering an oligonucleotide of the claimed invention with more than one cancer medicament can be found at least on page 101 lines 17-19 which state

> "Additionally, the methods of the invention are intended to embrace the use of more than one cancer medicament along with the immunostimulatory nucleic acids."

Support for the claimed genus of oligonucleotides that comprise SEQ ID NO:246 can be found at least on page 2 lines 28-29 which state that

> "The present invention relates in part to pyrimidine rich (Py-rich) and in some embodiments thymidine (T) rich immunostimulatory nucleic acids ..." ,

page 3 lines 8-9 which state

> "The Py-rich and TG immunostimulatory nucleic acids of the invention optionally include CpG motifs." ,

page 4, lines 28-30 which state that

> "In other embodiments the T rich nucleic acids are sequence selected from the group consisting of SEQ ID NO: ... 246, ... "

and page 19 lines 30-31 which state that

> "In one embodiment, the immunostimulatory nucleic acid is a CpG nucleic acid, wherein the CpG nucleic acid has a nucleotide sequence comprising SEQ ID NO:246."

The Examiner maintains that Applicant has not provided sufficient representative species to claim the genus of nucleic acids encompassed by the claims. The pending claims recite a genus of immunostimulatory oligonucleotides that share a common 24 base sequence motif. The written description of a genus can be satisfied in a number of ways including by "sufficient description of a representative number of species by ... disclosure of relevant, identifying characteristics, ... by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." MPEP 2163. The specification has provided the relevant identifying characteristic of the claimed genus (i.e., the 24 base sequence that is SEQ ID NO:246). The specification identifies this sequence as being immunostimulatory. Every species within the genus of nucleic acids "comprising SEQ ID NO:246" necessarily possesses this sequence. This would have been so recognized by the person of ordinary skill in the art.

Regarding SEQ ID NOs: 262, 273, 300, 305, 352, 412, 413, 429 and 891, which Applicant listed in the last Office Action response as examples of representative species of the claimed genus, the Examiner asserts that these species are not representative of the genus of oligonucleotides encompassed by the claims in terms of length, flanking sequence or backbone content. With respect to length and flanking sequence, SEQ ID NO:24 is 24 nucleotides in

length, while SEQ ID NOs:305 and 429 are each 30 nucleotides and differ from each other in the flanking sequence outside of the core sequence defined by SEQ ID NO:246. Each of these species has a different overall sequence, although each comprises the sequence of SEQ ID NO:246. Each of these is encompassed by the claimed invention.

The Examiner argues that the immunostimulatory nature of the claimed genus may be negatively impacted by flanking sequences. However, the Examiner has provided no rationale for this position. Applicant maintains that the art of immunostimulatory nucleic acids was sufficiently developed at the time of filing that one of ordinary skill in the art would recognize that flanking sequences could be added to a known immunostimulatory sequence (particularly one that is 24 bases long) without negative impact to the immunostimulatory activity. See for example U.S. Patents 6194388, 6207646, 6239116, 7271156 and 7402572. The Examiner's position is wholly inconsistent with the Patent Office's position, as evidenced by the granted claims of the recited patents, all of which were deemed adequately described by specifications similar to the instant specification.

With respect to backbone composition, SEQ ID NOs: 262, 273, 300, 352, 412, 413 and 891 represent species that differ from SEQ ID NO:246 in backbone content (see Table A). Thus, the specification contemplates species comprising SEQ ID NO:246 having differing backbone compositions.

The Examiner's assertion on page 4 of the Office Action, that Applicant relies on a "single species" is therefore incorrect. Applicant has provided sufficient structural information about the core 24 nucleotide sequence shared by oligonucleotides of the claimed genus, and Applicant has described a representative number of species to support the claimed genus. One of ordinary skill in the art would recognize from the original disclosure that Applicant was in possession of the claimed genus of oligonucleotides.

The Examiner further maintains that Applicant has not provided sufficient written description support for the claimed use of sequences comprising SEQ ID NO:246 and specific cancer medicaments. The Examiner asserts on page 5 of the Office Action that "Applicants' reliance on a generic disclosure of numerous oligonucleotides and numerous chemotherapeutic agents does not provide adequate direction or guidance to the currently claimed limitations". Applicant respectfully disagrees.

The specification does not merely disclose a laundry list of oligonucleotides. There is an explicit disclosure in the specification that an oligonucleotide corresponding to SEQ ID NO:246 is highly immunostimulatory. This is emphasized throughout the specification and Figures. Figures 4-10 all reveal immunostimulatory properties of SEQ ID NO:246 (ODN 2006). In the specification, page 25 lines 28-31 describe SEQ ID NO:246 as a "preferred embodiment", page 31, line 13 describes SEQ ID NO:246 as a "highly immune stimulatory CpG nucleic acid", page 32, line 4 describes SEQ ID NO:246 as a "highly immune stimulatory T-rich nucleic acid", page 133, lines 30-31 describes SEQ ID NO:246 as "very potent", and page 155, line 31 to page 156, line 1 discloses that SEQ ID NO:246 "showed the highest activity in human B cells and NK cells," and "was also the most active in stimulating chimpanzee and rhesus monkey B cell proliferation".

Furthermore, the specification discloses using an immunostimulatory oligonucleotide of the claimed invention with a cancer medicament such as a chemotherapeutic agent. Page 14 lines 27-31 teaches using Py-rich nucleic acids (of which SEQ ID NO:246 is a preferred example) with an anti-cancer therapy for increasing the responsiveness of a cancer cell to the cancer therapy. Page 19, lines 8-9 discloses that the immunostimulatory nucleic acid comprises SEQ ID NO:246. Page 15 lines 11-14 and page 100, lines 29-30 further disclose administering an immunostimulatory nucleic acid and an anti-cancer therapy that may be a chemotherapy. Page 15 line 16 through to page 16 line 18, Table C (page 104-107), page 107 line 3 and Table E (page 111-114) explicitly identify cisplatin, paclitaxel, doxorubicin, carboplatin and gemcitabine as chemotherapeutics. Page 101 lines 17-19 further discloses administering an oligonucleotide of the claimed invention with more than one cancer medicament. Cancer medicaments include chemotherapeutics (page 101 lines 15-16).

One of ordinary skill in the art, in light of the original disclosure, would appreciate that an oligonucleotide comprising SEQ ID NO:246 was highly immunostimulatory and would therefore be of use in a method for increasing the responsiveness to a cancer therapy. One of ordinary skill in the art would further understand from the disclosure of the specification that Applicant had contemplated and adequately described the use of an oligonucleotide comprising SEQ ID NO:246 with a cancer medicament such as carboplatin, doxorubicin, cisplatin, paclitaxel and gemcitabine.

The Examiner cites case law in support of this position that the claimed invention is not sufficiently supported by the specification. The instantly claimed invention and specification can be distinguished from each of these cases.

For example, in *In re Ruschig*, the claim at issue recited a compound which was not named or identified by formula in the specification. *In re Ruschig*, 154 USPQ 118 (CCPA 1967). The applicant in that case argued that one of ordinary skill in the art could arrive at the unnamed and unidentified subject matter by particular choices of variables presented in the specification. The instant case is readily distinguishable because it specifically and explicitly discloses the oligonucleotide class and the anti-cancer agents to be used to increase the responsiveness of a cancer cell. The ordinary artisan is provided with the "blaze marks" which are at least represented by the oligonucleotides having SEQ ID NO:246 and the named chemotherapeutic agents, all of which are explicitly disclosed and connected in the specification.

In *Fujikawa v. Wattanasin*, the Court found that a subgenus of a parent compound was not adequately described by disclosure of the parent compound itself. *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 (Fed. Cir. 1996). The subgenus required side groups which were not explicitly described in the specification. Rather, the specification taught other side groups that were preferred and these did not embrace those recited in the contested claim. Wattanasin's specification described a large genus of compounds without explicitly naming the specific subgenus of the claim and without explicitly reciting any species within that subgenus. Here too the instant case is distinguishable because it explicitly describes the genus of oligonucleotides and each of the chemotherapeutic agents recited in the claims, as outlined above. This is not an instance where broad genera are described without explicit identification of the claimed species within the described genus.

Unlike *Fujikawa*, the instant specification would "reasonably lead those skilled in the art to any particular species". Moreover, the Court in *Fujikawa* also stated that "specific claims to single compositions require reasonably specific supporting disclosure and while ... naming [each species] is not essential, something more than the disclosure of a class of 1000, or 100, or even 48 compounds is required." *Fujikawa*, 39 USPQ2d at 1905. The Court is apparently stating that naming each claimed species should be sufficient to satisfy the written description requirement. That is exactly what the instant specification does.

The Court in *Martin v. Mayer* stated that "the only inquiry is whether Mayer's disclosure contains, in accordance with the principles of section 112 paragraph 1, support for all material limitations of the claim as presented..." (emphasis added). *Martin v. Mayer*, 3 USPQ2d 1333, 1337 (Fed. Cir. 1987). The instant specification supports all the material limitations of the claims. It states that the class of oligonucleotides to which SEQ ID NO:246 belongs can be used in methods to increase the responsiveness of cancer cells to chemotherapeutics. It identifies SEQ ID NO:246 as a preferred oligonucleotide. It describes oligonucleotides comprising SEQ ID NO:246. It explicitly names the chemotherapeutics recited in the claims. As required by *Martin*, "persons of skill in the art will recognize that the applicant made the invention having these limitations" based on the disclosure in the instant specification. *Martin*, 3 USPQ2d at 1337.

The instant case can also be distinguished from *In re Smith*. *In re Smith*, 173 USPQ 679 (CCPA 1972). In that case, the Court affirmed the Board decision that a specification with "no mention" and "no disclosure" of one limitation (i.e., "at least 8 carbon atoms" or "8 to 36 carbon atoms") does not adequately describe these particular limitations and therefore does not support the claims that recite these limitations. *Smith*, 173 USPQ at 683, 684. The specification in *Smith* provided a generic disclosure of the claimed compounds and specifically disclosed some of the species within the claimed subgenus. Neither was sufficient to support the claimed subgenus. *Smith*, 173 USPQ at 683. These facts can be contrasted with the instant claims which recite a genus of oligonucleotides and specific chemotherapeutics, both of which are explicitly disclosed in the specification.

The Examiner has cited no case law to show that a specification that describes all the limitations contained within a claim does not support such a claim. To reiterate, the instant specification explicitly identifies the claimed method of increasing the responsiveness to an anti-cancer agent using a Py-rich nucleic acid with an anti-cancer agent, that Py-rich nucleic acids include T-rich nucleic acids and that such T-rich nucleic acids may also be CpG nucleic acids, that SEQ ID NO:246 is both a T-rich and a CpG nucleic acids, nucleic acids that comprise SEQ ID NO:246, and carboplatin, cisplatin, doxorubicin, gemcitabine and paclitaxel as anti-cancer agents to be used in combination with the immunostimulatory oligonucleotides of the invention. The instant specification therefore does not disclose a mere generic "forest"; rather it explicitly

discloses and identifies the trees within the forest and provides the blaze marks between such trees. The claimed invention is thus adequately described.

Reconsideration and withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. §103

The Examiner rejected claims 121-142 under 35 U.S.C. §103(a) as being unpatentable over Wagner et al. (US 2004/0235778) in view of Maxwell et al. (Seminars in Oncology Nursing, 8(2):113-123, May 1992). Applicant respectfully traverses.

Applicant asserts that a *prima facie* case of obviousness has not been made because there is no motivation to combine these references, there would have been no reasonable expectation of success in doing so, and even if the references could be properly combined their combination would not yield every limitation of the rejected claims.

Wagner et al. discloses that IL3/GM-CSF/IL-5 are "Th0 and Th2 cytokines" [0019]. Wagner et al. discloses that in contrast CpG oligonucleotides stimulate a Th1 response and are Th2 suppressive [0017, 0029 and 0090]. Wagner et al. describes GM-CSF/IL-5 as "dispensable for hematopoiesis" [0019]. Moreover, Wagner et al. discloses that when an oligonucleotide, that had previously been shown to cause splenomegaly and hypergammaglobulinemia, was administered in vivo in mice, there was an upregulation of certain cytokines, but "no significant differences in splenic mRNA levels" of GM-CSF were detected [0017]. One of ordinary skill in the art, in light of Wagner et al., would appreciate that CpG oligonucleotides are immunostimulatory but that they act through a different mechanism than by induction of GM-CSF. Wagner et al. does not disclose coadministering an immunostimulatory oligonucleotide corresponding to SEQ ID NO:246 with carboplatin, paclitaxel, doxorubicin, cisplatin or gemcitabine.

Maxwell et al. also does not disclose combining an immunostimulatory oligonucleotide with any of these chemotherapeutic agents nor does this reference, when viewed as a whole, provide a reason or suggestion to do so. Maxwell et al. discloses the preferential use of hematopoietic growth factors to lessen myelosuppression which occurs as a side effect to chemotherapy. Specifically, Maxwell et al. highlights the use of the growth factor GM-CSF and discusses its success in clinical trials. On page 119, Maxwell et al. states "It is difficult not to be

impressed with the results of the studies thus far. Growth factors have the potential to minimize the degree and duration of myelosuppression ..." One of ordinary skill in the art, in light of Maxwell et al. would appreciate that growth factors such as GM-CSF were effective in minimizing myelosuppression.

There would have been no reason to combine these two references since Maxwell et al. did not suggest the use of CpG ODNs, and instead taught the use of growth factors such as GM-CSF and Wagner et al. taught the distinctions between immune induction by CpG ODNs and by growth factors such as GM-CSF. Moreover, based on these disclosures, one of ordinary skill in the art would not have had a reasonable expectation of success in combining the teachings of the references. Even if the references could be combined, and Applicant maintains they properly cannot, the combination does not teach that the responsiveness of a cancer to an anti-cancer therapy such as a chemotherapy can be increased by combination with an immunostimulatory oligonucleotide.

The Examiner has cited case law in support of the position that the recognition of an advantage that "would flow naturally from following the suggestion of the prior art cannot be the basis for patentability." The claims in both *Ex parte Obiaya* and *In re Wiseman and Kovac* were directed to articles of manufacture and applicants in those cases argued non-obviousness based on unexpected properties that were not recited in the claims. *Ex parte Obiaya*, 227 USPQ 58 (Bd. Pat. App. & Inter. 1985); *In re Wiseman and Kovac*, 201 USPQ 658 (CCPA 1979). The explicit limitations of the claims however were determined to be present in the prior art references relied upon, and it was found that such references could be combined. The instant situation is clearly distinguishable. The instant claims are method claims that recite at least one limitation that is not taught nor suggested by either of the cited references (i.e., the ability to increase the responsiveness to an anti-cancer agent). Therefore, unlike the references in *Obiaya* and *Wiseman*, the instantly cited references do not provide all the limitations of the rejected claims. To be clear, the issue in *Obiaya* and *Wiseman* was one of unexpected, unclaimed properties, while the issue in the instant case is that the combination of the references does not yield all of the explicitly recited claim limitations. The Examiner's approach has apparently read the preamble out of the claims, and this is legally incorrect.

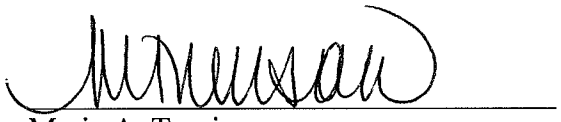
Reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,



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